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Alleviating visceral cancer pain in patients with pancreatic cancer using cryoablation and celiac plexus block ☆

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ABSTRACT

Little is known about the effects of pancreas cryoablation (PCA) on abdominalgia in pancreatic cancer patients or its synergism with celiac plexus block (CPB). In patients without abdominalgia, to investigate the effects of PCA; in patients with abdominalgia, to investigate the pain-alleviating effects of PCA + CPB. Sixty-two patients were enrolled in this retrospective review; 12 without abdominalgia refused PCA, 15 without abdominalgia received PCA to reduce their tumor load and 35 with abdominalgia received PCA + CPB to reduce tumor load and alleviate pain. All PCA and PCA + CPB procedures were performed successfully. Some slight adverse effects (e.g. increased serum amylase, abdominal distension and nausea, abdominal bleeding) had disappeared by 3 weeks, spontaneously or after symptomatic treatment. In patients without abdominalgia, pain occurred in one-third of cases (all with pancreatic head cancer) after PCA but had stopped 1–12 days after treatment; in patients with abdominalgia before treatment, pain stopped immediately after PCA + CPB in 18 cases and 2–24 days after treatment in 17 (all with pancreatic head cancer); a significant difference was found between pretreatment and post-treatment pain frequency ($P = 0.0019$), regardless of the presence of advanced ($P = 0.0096$) or metastatic ($P = 0.0072$) cancer. The average time to pain relief was approximately 7 days after both PCA and PCA + CPB, and abdominalgia did not recur for more than 8 weeks. PCA may cause short-term pain in some pancreatic cancer patients. Combined PCA + CPB can alleviate cancer pain for more than 8 weeks, without severe side effects.

Introduction

The prevalence of pain in cancer is estimated at 25% for those newly diagnosed, 33% for those undergoing active treatment and greater than 75% for those with advanced disease [22]. It is estimated that pain occurs in 80–85% of patients with unresectable pancreatic tumors [19,32]. Perineural invasion is a prominent characteristic of pancreatic cancer, and pain is an important consequence of perineural invasion [3]. Traditional pain medications such as analgesics, opiates and non-steroidal anti-inflammatory drugs are somewhat effective in the treatment of pancreatic cancer pain. However, these drugs must be taken daily, leading to increasing resistance to their actions, and side effects (e.g. insomnia, anorexia, nervousness, tachycardia, dry mouth) can affect patient's quality of life [16,17]. Neurolytic celiac plexus block (CPB) as a means to relieve visceral cancer-related pain using ethanol has been reported to be effective in 74% of patients [24], but has many undesirable side effects (e.g. orthostatic hypotension, transient diarrhea, interscapular back pain, reactive pleurisy) [7].

Cryosurgery is a novel therapeutic approach to the treatment of benign and malignant tumors, especially unresectable tumors [9]. Under the guidance of imaging technology, percutaneous pancreas cryoablation (PCA) has been reported to be ideal in terms of effectiveness (reducing tumor load and extending life span) and safety (fewer severe adverse effects) [29,30]. Cryotherapy for analgesia has been used since 1976 and has been shown to effective and safe [10,15]. Combining cryoablation of the celiac plexus with image guidance has been postulated to further reduce the risk of complications when alleviating intractable pain caused

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by pancreatic cancer [33]. In contrast to both medical treatment and other invasive procedures (e.g. neurectomy), significant pain relief is achieved acutely with cryoablation and the recovery period is relatively brief [27]. However, most of the available literature on cryoablation-associated analgesia comprises case reports. In the present study, our single-center experience of pain relief in pancreatic cancer was reviewed retrospectively. In patients without abdominalgia, the effects of PCA were investigated; in patients with abdominalgia, the pain-alleviating effects of PCA + CPB were investigated.

Methods

Ethics

The study protocol received ethical approval from the Regional Ethics Committee of Guangzhou Fuda Cancer Hospital. Written informed consent was obtained from each participant in accordance with the Declaration of Helsinki.

Patient selection

This was a retrospective study of patients treated for advanced or metastatic pancreatic tumors in our cancer hospital from April, 2011 through August, 2012. Their diagnoses were principally based on computed tomography (CT) imaging, with CT-guided needle biopsy for histologically definitive diagnosis of pancreatic adenocarcinoma [28]. Surgery and chemotherapy were deemed inappropriate under any of the following conditions: multifocal disease, unresectable pancreatic tumor, patient refused to undergo surgery and chemotherapy or was seeking further treatment after failure of chemotherapy, severe complications (e.g. hypertension, hydrothorax, ascites), brain metastasis and advanced age. The inclusion criteria were as follows: Karnofsky performance status score $\geqslant 70$; platelet count $\geqslant 80 \times 10^9$/l; white blood cell count $\geqslant 3 \times 10^9$/l; neutrophil count $\geqslant 2 \times 10^9$/l; hemoglobin $\geqslant 90$ g/l; prothrombin time international normalized ratio $\geqslant 1.5$; diameter of largest primary or metastatic tumor <6 cm (as measured on preoperative CT); pancreatic tumor not obviously invading the main pancreatic duct, inferior vena cava, duodenum or colon; absence of level three hypertension, severe coronary disease, myelosuppression, respiratory disease and acute or chronic infection; and adequate hepatic function (bilirubin <30 μM, aminotransferase <60 U/l) and renal function (serum creatinine <130 μM, serum urea <10 mM). The study involved 62 patients who met our inclusion criteria and for whom we could obtain complete information over an 18-month perio7d of clinical treatment.

Pain medication principles and programs

Clinical practice guidelines developed by the National Comprehensive Cancer Network [20] and the American Pain Society [1] emphasize the essentiality of comprehensive pain assessment. Initial and ongoing assessment of pain includes the evaluation of pain intensity using a visual analog scale (VAS) ranging from 0 (indicating no pain) to 10 (indicating the worst pain imaginable). In our hospital, pain scores of 5–10 are defined as moderate to severe pain, and our medication principles and programs reference international practices as follows [16,18,22]. (i) According to the degree and pattern of pain, analgesics such as Oxycontin or MS Contin are delivered at the first available opportunity to control pain below the pain threshold. (ii) In patients with mild pain, non-steroidal anti-inflammatory drugs (e.g. ibuprofen, celecoxib) are optional. If the results with these are not good, weak opioid drugs (e.g. tramadol, fentanyl) are added; if the pain continues, strong opioid drugs (e.g. morphine, pethidine hydrochloride) are used. (iii) For moderate to severe pain, two or more analgesics are combined to enhance pain relief and reduce drug consumption and complications. (iv) Analgesics are used alternately to prevent the development of resistance, and doses increased from low to high until the pain stops. (v) The side effects of pain medication are actively prevented and controlled.

All episodes of newly emerging moderate to severe pain (VAS score 0–3) were quickly relieved by opioid drugs. The occurrence and scores for abdominalgia (VAS score 5–10) were recorded in detail, including pretreatment (from day 5 to day 0) and post-treatment (from day one to complete relief of abdominalgia). Because abdominalgia is the predominant type of pancreatic tumor pain, other types of pain (e.g. at puncture sites, celiac lymph nodes, metastatic lesions) were not included in this study. Purgative medicines were provided generally to all patients to prevent constipation.

Pca

Cryoablation procedures were performed under double-row helical CT (Somatom Emotion Duo; Siemens, Germany) or color ultrasound (ALOKA SSD-5500SA; Aloka, Japan) guidance. Before cryosurgery, patients were administered general anesthesia and positioned for an upper abdominal incision. Based on the location of the pancreatic tumor, 1.7 mm cryoprobes (Cryo-42; Endocare, Irvine, CA, USA) were inserted percutaneously via the retroperitoneal, transhepatic or transgastric approach using an argon gas-based cryosurgical unit (Endocare) for cryoablation of different parts of the tumor [21]. For tumors greater than 3 cm in longest diameter, more than one cryoprobe was used. Care was taken not to puncture the main pancreatic duct and duodenum, by directing the probes away from the inferior vena cava. All pancreatic tumors underwent a two freeze–thaw cycle procedure (commonly freezing for 10 min and natural warming for 10 min, then repeat the process) performed by Dr. L.Z. Niu, as described previously [5,29,30].

Patients with primary or metastatic tumors of diameter $\geqslant 6$ cm or tumors that were obviously invading the main pancreatic duct, postcava, duodenum or colon were treated by other means [2,31] and were not enrolled in this study.

For some patients with irregular cancer shape, iodine-125 seeds (Syncor Pharmaceutical, Shanghai, China) were used for brachytherapy and inserted percutaneously before cryosurgery using a three-dimensional treatment-planning system. The seeds (single seed activity, 0.7 mCi; half-life, 3 months) were implanted along the tumor border at intervals of 0.5 cm to a total dose of approximately 120 Gy. In most cases, $\leqslant 20$ particles were used.

Once cryoablation was completed, 1 ml of fibrinogen and thrombin for each probe was injected into the sheath simultaneously. Patients were then observed in the intensive care unit for at least 6 h and fasted for at least 24 h. Therapies against infection and to inhibit pancreatic juice secretion were given for a few days. Patients who underwent cryosurgery by the transgastric approach received antacid and stomach mucosa-protecting drugs for a few days; patients in whom the transhepatic approach was used received antihemorrhagic, abdominal belt for hemostasis and liver-protecting drugs.

Neurolytic CPB

Details of the transintervertebral disc approach for neurolytic CPB were as described previously [11,12]. Local anesthetic (1% lidocaine, 5 ml) was injected at the needle insertion sites, which were 2.5–5.0 cm from the midline at the T11–L1 intervertebral disc level. Under CT guidance, a 15-cm 23-G needle was then inserted

through the predetermined insertion site toward the intervertebral disc, in the predetermined direction. When the tip of the needle encountered the disc, the needle was advanced until the tip penetrated it. After confirmation of the needle placement with a CT scan, confirmation of loss of resistance, and no aspiration of blood, 1 ml 10% lidocaine with 4 ml contrast medium was injected. If the spread in the target area was sufficient and the pain relief satisfactory, 5–15 ml of 99.5% ethanol was injected through each needle 30 min after the lidocaine injection. If the spread of contrast medium and pain relief were insufficient, additional needles were inserted until satisfactory pain relief was achieved. The dose of alcohol was determined according to the general condition of the patient and the spread of the contrast medium.

Statistical analysis

Unpaired Student's *t*-tests were used to compare the numbers of episodes of pain and numbers of days to pain relief in patients with advanced or metastatic cancer. Paired Student's *t*-tests were used to compare the numbers of episodes of pain in patients before and after treatment. All statistical analyses were conducted using GraphPad Prism 5 (GraphPad Software, San Diego, CA, USA). $P < 0.05$ was considered to indicate a statistical difference; $P < 0.01$ was considered to indicate a significant difference.

Results

Patient data and numbers of episodes of abdominalgia

During the 18-month study period (from April, 2011 to August, 2012), 62 patients (42 men and 20 women; age range, 27–84 years; average age, 56 years; 21 patients from the Middle East, 22 from Southeast Asia and 19 from China) were diagnosed with pancreatic cancer in our hospital (17 with advanced cancer and 45 with metastatic cancer). Twenty-seven patients had no pain (eight with advanced cancer and seven with metastatic cancer; nine tumors in the pancreatic head, three in the pancreatic body and three in the pancreatic tail) and received PCA only (Table 1). Thirty-five patients had moderate to severe pain (six with advanced cancer and 29 with metastatic cancer; 22 tumors in the pancreatic head, six in the pancreatic body and seven in the pancreatic tail); all underwent PCA + CPB (Table 2). More patients with metastatic cancer (64.44%) had pain than did those with advanced cancer (35.29%); before treatment, the number of episodes of pain in patients with advanced cancer (6.167 ± 1.249, $n = 6$) was higher than that in patients with metastatic cancer (7.931 ± 1.952, $n = 29$; $P = 0.6894$ on unpaired *t*-test).

Perioperative outcomes

PCA and CPB were performed successfully in 50 patients. No severe complications (e.g. pancreatic fistula, bile leakage, intestinal fistula) occurred after cryoablation. All common adverse effects are listed in Tables 1 and 2 and were treated symptomatically. Five patients (10%) with abdominal pain and fever were diagnosed with acute pancreatitis, but recovered in 9–17 days. Fourteen patients (28%) had raised serum amylase on the first day after the procedure, unaccompanied by ascites or leukocytosis, but returned to normal in the following 5 days. In five patients (10%) with diabetes, fasting blood glucose levels increased to 20–25 mM on the first day after PCA, but were well controlled with insulin injections. A mild decrease in platelet count occurred in eight patients (16%), but the count returned to normal within 8–13 days without treatment. Abdominal distension and nausea occurred in 14 patients (28%) on the first day after cryoablation, but resolved spontaneously on

Table 1
Data for patients without abdominalgia who received percutaneous pancreas cryoablation only.

No.	Admission date	Cancer stage	Gender/ Age	Tumor location	Number of episodes of abdominalgia from day −5 to day 0 of treatment	Number of episodes of abdominalgia from day 1 of treatment to complete abdominalgia relief	Days from day 1 of treatment to complete abdominalgia relief	Adverse effects
1	4/1/2011	III	F/57	Head	0	2	9	Fever, amylase increase, abdominal bleeding
2	7/23/2011	I	M/61	Tail	0	0	0	Abdominal distension/nausea
3	8/6/2011	III	M/65	Body	0	0	0	
4	8/9/2011	IV	M/38	Head	0	3	4	Amylase increase, platelet decrease, abdominal bleeding
5	8/23/2011	II	F/61	Head	0	2	1	Amylase increase, platelet decrease, abdominal bleeding
6	9/14/2011	II	F/49	Body	0	0	0	Ascites
7	10/12/2011	IV	F/60	Head	0	0	0	Abdominal distension/nausea
8	10/27/2011	IV	F/69	Head	0	0	0	
9	12/7/2011	I	M/58	Tail	0	0	0	Abdominal distension/nausea
10	1/19/2012	IV	M/52	Body	0	0	0	
11	4/11/2012	IV	F/27	Head	0	6	12	Fever, amylase and blood glucose increase, abdominal bleeding
12	7/11/2012	IV	M/56	Tail	0	0	0	Ascites
13	7/26/2012	III	M/41	Head	0	10	10	Fever, amylase increase
14	7/28/2012	I	F/84	Head	0	0	0	Abdominal distension/nausea
15	8/8/2012	IV	M/66	Head	0	0	0	Abdominal distension/nausea

Table 2
Data for patients with abdominalgia who received percutaneous pancreas cryoablation plus celiac plexus block.

No.	Admission date	Cancer stage	Gender/ Age	Tumor location	Number of episodes of abdominalgia from day –5 to day 0 of treatment	Number of episodes of abdominalgia from day 1 of treatment to complete abdominalgia relief	Days from day 1 of treatment to complete abdominalgia relief	Adverse effects
1	4/6/2011	IV	F/46	Head	22	5	24	Abdominal distension/ nausea, abdominal bleeding
2	6/8/2011	IV	F/54	Head	6	2	2	Abdominal distension/ nausea
3	6/8/2011	IV	F/54	Head	6	4	16	
4	6/28/2011	IV	F/65	Head	18	6	17	Fever, amylase increase, platelet decrease, abdominal distension/nausea, abdominal bleeding
5	7/12/2011	IV	F/43	Head	12	17	14	Abdominal distension/ nausea, abdominal bleeding
6	8/11/2011	IV	F/68	Body	3	0	0	Ascites
7	8/24/2011	IV	F/68	Tail	50	0	0	
8	9/13/2011	IV	M/53	Body	2	0	0	Ascites
9	9/19/2011	IV	F/66	Head	1	2	7	Amylase increase, platelet decrease, ascites
10	10/7/2011	IV	F/58	Body	6	0	0	
11	10/13/2011	IV	M/58	Head	3	3	7	Amylase increase, platelet decrease, abdominal distension/nausea, ascites
12	10/18/2011	I	F/45	Head	9	0	0	
13	11/3/2011	IV	F/58	Head	3	0	0	
14	11/8/2011	IV	M/47	Head	1	0	0	
15	11/27/2011	III	M/59	Head	6	4	6	Amylase and blood glucose increase, ascites
16	11/29/2011	IV	M/63	Tail	3	0	0	
17	12/1/2011	IV	F/53	Head	4	0	0	Amylase increase, platelet decrease
18	12/14/2011	IV	F/58	Head	13	4	3	Amylase and blood glucose increase
19	12/25/2011	IV	M/44	Head	4	1	5	
20	2/3/2012	IV	F/54	Head	8	2	10	Fever, amylase increase, abdominal distension/ nausea, abdominal bleeding
21	3/13/2012	IV	M/67	Head	2	8	5	Ascites, abdominal bleeding
22	3/31/2012	IV	F/68	Tail	3	0	0	
23	4/13/2012	IV	F/70	Tail	1	0	0	
24	4/21/2012	IV	F/37	Head	2	3	3	Amylase and blood glucose increase
25	5/1/2012	III	M/65	Head	8	2	5	Ascites, abdominal bleeding
26	5/25/2012	III	F/50	Head	9	3	14	Ascites, abdominal bleeding
27	5/28/2012	IV	F/72	Body	8	0	0	Abdominal distension/ nausea
28	6/5/2012	I	M/57	Head	3	0	0	
29	6/10/2012	IV	M/45	Tail	1	0	0	
30	6/26/2012	III	F/66	Body	2	0	0	Ascites
31	6/29/2012	IV	F/71	Tail	1	0	0	Abdominal distension/ nausea
32	7/13/2012	IV	F/46	Tail	15	0	0	Ascites
33	8/2/2012	IV	F/41	Body	3	0	0	
34	8/8/2012	IV	M/50	Head	2	4	4	Abdominal distension/ nausea
35	8/15/2012	IV	F/57	Head	27	4	9	Amylase and blood glucose increase, abdominal distension/nausea, ascites

the following day. Thirteen patients (26%) complained of poor appetite and were diagnosed with ascites on ultrasonography; this improved in the following 3–5 days without treatment. Abdominal bleeding occurred in 11 patients (22%), but improved in the following 7 days. Fever developed in 16 patients (32%), but resolved spontaneously in the following 3 days. No treatment-related deaths or conversions to chemotherapy occurred.

PCA in patients without abdominalgia

Of the 15 patients who did not have abdominalgia on admission and underwent PCA only, 10 remained abdominalgia-free after cryosurgery and five suffered multiple episodes of moderate to severe abdominalgia (VAS score $\geqslant 5$ on two, two, three, six and 10 occasions, respectively; all had pancreatic head cancer; Table 1). There was no difference in the number of episodes of abdominalgia before and after treatment overall (0 vs. 1.53 ± 2.9; $P = 0.0598$; Fig. 1A) or among patients with advanced cancer (0 vs. 1.75 ± 3.45; $P = 0.1949$; Fig. 1B left) or metastatic cancer (0 vs. 1.29 ± 2.36; $P = 0.1996$; Fig. 1B right). In the patients with pancreatic head cancer (three advanced and two metastatic) with new abdominalgia, the time taken for pain relief was 1, 9, 4, 12 and 10 days, respectively. The average time to pain relief was approximately 7 days. Abdominalgia had not recurred by the 8-week follow-up visit.

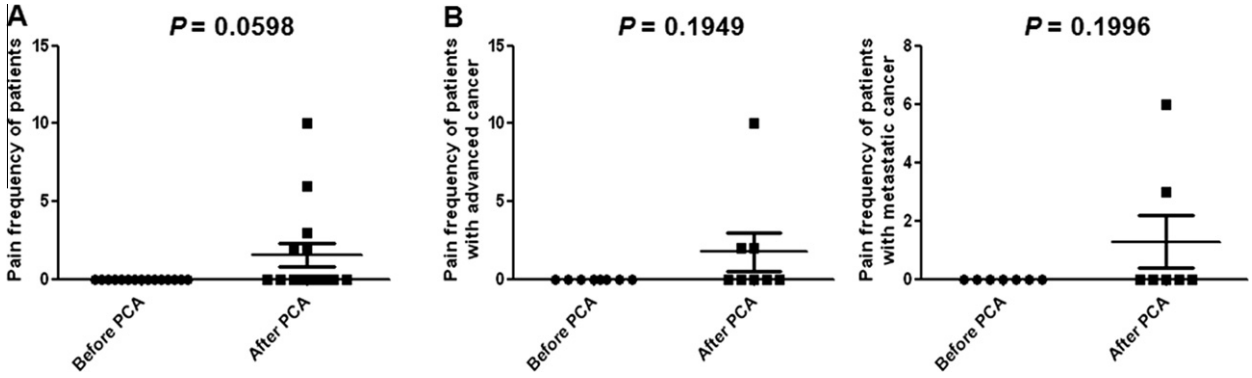

Fig. 1. Number of episodes of post-treatment abdominalgia in patients without pretreatment pain. Paired *t*-tests were used for all comparisons. (A) Data for all 15 patients. (B) Data for eight patients with advanced cancer and seven patients with metastatic cancer. Horizontal lines represent the mean and standard deviation.

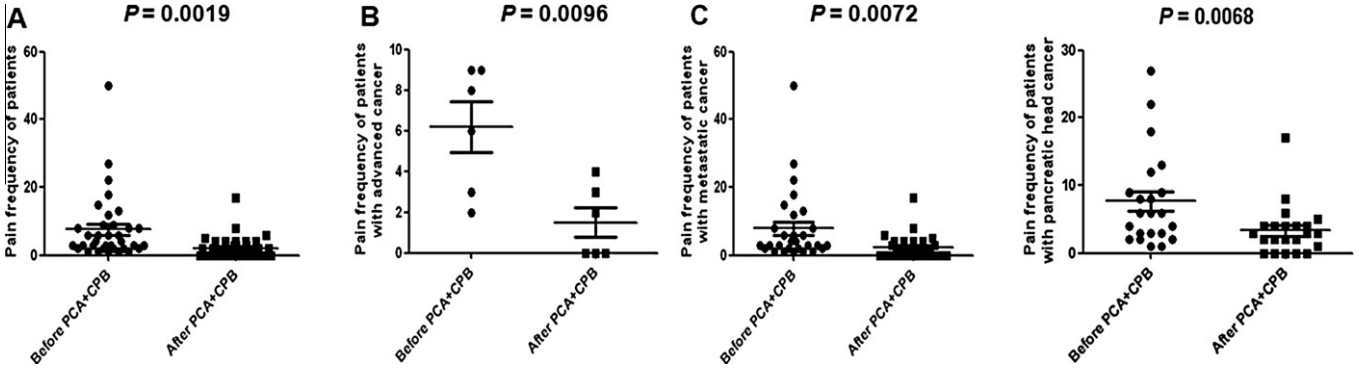

Fig. 2. Number of episodes of post-treatment abdominalgia in patients with pretreatment pain. Paired *t*-tests were used for all comparisons. (A) Data for all 35 patients. (B) Data for six patients with advanced cancer and 29 patients with metastatic cancer. (C) Data for 22 patients with pancreatic head cancer. Horizontal lines represent the mean and standard deviation.

PCA+CPB in patients with moderate to severe abdominalgia

In 18 of the 35 patients who had abdominalgia on admission and underwent PCA + CPB, abdominalgia disappeared immediately after treatment. Seventeen patients suffered multiple episodes of moderate to severe abdominalgia (VAS score $\geqslant 5$ on two occasions in four patients, three in three patients, four in five patients, and 1, 5, 6, 8 and 17 in five patients, respectively; Table 2) that were alleviated 9 ± 6 days later. There was a significant difference in the occurrence of abdominalgia before and after treatment overall (7.63 ± 9.63 vs. 2.11 ± 3.35; $P = 0.0019$; Fig. 2A) and in patients with advanced cancer (6.17 ± 3.06 vs. 1.5 ± 1.76; $P = 0.0096$) or metastatic cancer (7.93 ± 10.51 vs. 2.24 ± 3.6; $P = 0.0072$; Fig. 2B). The number of episodes of pain in patients with pancreatic head cancer decreased significantly (7.68 ± 6.98 vs. 3.36 ± 3.71; $P = 0.0068$; Fig. 2C), but abdominalgia disappeared immediately after treatment in patients with pancreatic body or tail cancer (Table 2). Among the patients with pancreatic head cancer with continuing abdominalgia, the time to pain relief was 2–24 days; there was no difference between patients with advanced cancer (5 ± 5.74 days, $n = 5$) and those with metastatic cancer (7.41 ± 6.85 days, $n = 17$; $P = 0.4836$ on unpaired *t*-test; Table 2). The average time to pain relief was approximately 7 days. Abdominalgia had not recurred by the 8-week follow-up visit.

Discussion

Perineural invasion is a prominent characteristic of pancreatic cancer, being a route for metastatic spread and a source of pain [3]. Invading cancer cells damage the neuronal sheath, leaving nerve synapses vulnerable to noxious stimuli from the extracellular matrix, and signaling between pancreatic cancer cells and nerves leads to accelerated growth of pancreatic cancer cells and nerve growth and enlargement [4,8]. Most cases of pancreatic cancer are found because of jaundice; other important signs are abdominal pain, nausea/vomiting, constipation, diarrhea, weight loss, malaise and new-onset diabetes [25]. In our experience, pain generally increases as the disease progresses, gradually becoming moderate to severe [29,30]; there is no difference in the frequency of pain between advanced and metastatic pancreatic cancer. Back pain (which could be due to metastases in lymph nodes or other organs) and puncture point pain are also common; however, this study focused on alleviating abdominal pain, predominantly by PCA.

Traditional approaches to the relief of cancer pain include radiation therapy, hormonal therapy and chemotherapy, palliative surgery, and opioid and non-opioid analgesics. However, it has been reported that only 50% of patients with metastatic cancer have adequately controlled pain [26]. Use of cryoablation for palliation of pain has also been reported. Kovach et al. performed intraoperative cryosurgery on nine patients with unresectable pancreatic cancer, with no deaths or major complications; following the treatment, pain was alleviated in all cases [13]. In our previous retrospective analysis of a large sample of patients, pain relief was universal after cryosurgery [5].

In the present study, we performed a retrospective review of our hospital's database to evaluate changes in abdominalgia in patients who underwent PCA and/or CPB, according to disease stage and pain level before treatment. Interestingly, five patients (33%)

without pretreatment abdominal pain suffered moderate to severe pain after PCA (Fig. 1A), abdominalgia disappeared immediately after PCA + CPB in 18 patients (51%) (Fig. 2A), and 17 of the 22 patients who suffered moderate to severe abdominalgia after treatment had tumors in the pancreatic head. In pancreatic head cancer (the most common type of pancreatic cancer), the tumor is close to the celiac plexus and the surrounding cavity is narrow, which can lead to persistent pain from compression or distraction [34]. Cryoablation inactivates tumor cells and tumor-eroded nerves, but tissue edema or hemorrhage [6,14,21] shortly after the procedure may increase compression of the celiac plexus and cause severe pain. Thus, PCA was used in combination with CPB in the present study to relieve cancer pain quickly and achieve a long-term effect.

In patients who had never suffered abdominal pain and those who had pretreatment abdominalgia only, these treatments seemed to be safe and effective. Pain that emerged post-treatment in patients who had no pain preoperatively may have been associated with pancreatic head tumor (all five patients), acute pancreatitis (three patients), tumor edema (all five patients), abdominal bleeding (four patients) or all of these factors (two patients; Table 1). Fortunately, pain occurred in only one-third of previously pain-free patients and there was no difference in the overall number of episodes of pain before and after treatment ($P = 0.0598$, not affected by tumor stage). An additional 2.4 days was needed for the pain-relieving treatment to take effect, and it may be difficult to shorten this time significantly because regression of edema in frozen parts takes time, and stretching stimuli to the celiac plexus are a major cause of abdominal pain.

In patients with moderate to severe abdominalgia preoperatively, continued pain post-treatment may have been associated with pancreatic head tumor (all 17 patients), acute pancreatitis (two patients), tumor edema (all 17 patients), abdominal bleeding (seven patients) or all of these factors (two patients; Table 1). Abdominal pain may decline gradually with absorption of edema. Encouragingly, pain stopped immediately after treatment in half of the patients and there was a significant difference in overall pain frequency before and after treatment ($P = 0.0019$, not affected by tumor stage). Despite a significant decrease in the number of episodes of pain after treatment of pancreatic head cancer ($P = 0.0068$; Fig. 2C), an additional 7 days was often needed for pain relief; this interval may be shortened with improvements in perioperative care. These results show that, as well as effectively reducing tumor load, PCA + CPB can reduce patients' suffering.

The limitations of this study should be noted. First, though the tumor location was classified as pancreatic head, body or tail, the degree of invasion into the main pancreatic duct, outer membrane and celiac plexus were not studied in detail. Second, in most cases, brachytherapy (iodine-125 seed implantation) was performed along with cryoablation to enhance the killing effect [5,21,29,30]. Given the small radius of action of iodine-125 seeds, which were implanted at the border of tumor, and the sensitivity of nerves to radiation, brachytherapy can play only a supporting role in pain relief by cryoablation [23]. The effects of brachytherapy for pancreatic cancer pain need to be further investigated. Third, in addition to the pancreatic tumor itself, severe pain can be caused by metastases to celiac lymph nodes and other organs as well as the cryoprobe puncture, and these sources need to be addressed together with pancreatic pain. Fourth, the VAS method of pain evaluation has a degree of subjectivity; thus, instead of measuring precise pain scores, we counted the numbers of episodes of pain.

In conclusion, imaging-guided percutaneous PCA with or without CPB is an effective and safe method for the management of pain in patients with advanced or metastatic pancreatic cancer. In patients with unresectable pancreatic cancer who refuse chemotherapy, this method is a new treatment option that offers relief from severe pain, improving quality of life and survival time. These procedures are at an early stage of development, however, and need to be further improved and optimized.

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